OWENS CORNING SCIENCE & TECHNOLOGY CENTER
2790 COLUMBUS ROAD, ROUTE 16
GRANVILLE, OHIO 43023
740.321.7228 FAX 740.321.4228
INTERNET: john.hadley@owenscorning.com

JOHN G. HADLEY, Ph.D.
DIRECTOR OF TOXICOLOGY

OWENS CORNING
INNOVATIONS FOR LIVING

VIA E-MAIL AND OVERNIGHT MAIL

June 7, 2010

Dr. Ruth Lunn
Director, Report on Carcinogens
National Toxicology Program
National Institute of Environmental Health Sciences
MD KY-14
530 Davis Drive
Morrisville, NC 27560

Re: Comments from John G. Hadley, Ph.D., Owens Corning Corporation

Dear Dr. Lunn:

I appreciate the opportunity to comment on the Draft Substance Profile for Glass Wool Fibers. By way of background, I have been involved in fiber health effects research for over 20 years, and I was co-study director on the chronic inhalation studies of insulation glass wools MMVF 10 and MMVF 11. I have also co-authored numerous papers on the role of durability on the health effects of glass fibers (Appendix A). Finally, I serve as the Chair of the Health and Safety Advisory Subcommittee for the North American Insulation Manufacturers Association ("NAIMA"), and I endorse NAIMA's comments submitted under separate cover.

My comments will focus on several issues where the scientific accuracy of the Draft Substance Profile could be improved in order to provide a Final Substance Profile that contains clear and actionable information and data.

BIOPERSISTENCE AND DISSOLUTION RATES

It is well established that the biopersistence of fibers is the critical determinate of their potential to cause chronic health effects. The extensive database on this topic is reviewed in Maxim, L.D., Hadley, J.G., et al. (2006).[1]

[1] Maxim, L.D., Hadley, J.G., Potter, R.M., and Niebo, R., "The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology," *Regulatory Toxicology and Pharmacology*, 46(1): 42-62, pp. 54-55 (2006).

While the Draft Substance Profile discusses briefly some of the relevant biopersistence information, it contains an incomplete and misleading discussion regarding the use of *in vitro* dissolution rates to predict the *in vivo* carcinogenicity hazard of fibers in animals.

On pages 4-5 concerning the Eastes/Hadley model paper, the Draft Substance Profile states:

> A mathematical model relating the K_{dis} to fiber carcinogenicity and fibrosis provided evidence that K_{dis} values at pH 7.4 could be used to predict tumorigenicity for inhalation exposure ($P = 0.16$ chi-square test, no significant disagreement between the model and the data). . .

Yet, three sentences later, the Draft Substance Profile states:

> However it is unclear whether dissolution rate can accurately predict the carcinogenicity of a specific fiber. For example, although the reported K_{dis} for the respirable insulation fiber MMVF 10 (122.4 ng/cm^2 per hour) was higher than that for the special-purpose fiber JM 100/475 (9.1 ng/cm^2 per hour), the incidence of mesothelioma in rats exposed by the intraperitoneal injection was higher for the insulation fiber (59%) than for the special-purpose fiber (33%) (Miller *et al.* 1999).

It is important to consider the following when determining the relevance and scientific validity of the above statement.

First, in the cited Miller paper,[2] ("Miller 1999a") the dose in the intraperitoneal study for the more soluble insulation wool fiber was 17.4 times higher than the special purpose fiber (144.4 mg for MMVF 10 versus 8.3 mg for JM 100/475). It is inappropriate to suggest that dissolution rate is not reliable while failing to mention the massive dose difference between the two groups. If the Draft Substance Profile had disclosed this nearly 20 times difference in dose, the statement questioning the utility of dissolution rate perhaps would likely be tempered.

Second, a companion paper by Miller, *et al.* entitled "Influence of characteristics of inhaled fibres on development of tumors in the rat lung,"[3] ("Miller 1999b") is not cited in the Draft Substance Profile, but is actually more relevant as those animals were exposed by inhalation and not intraperitoneal injection whose utility was challenged by the IARC 2002 Monograph, the NTP June 2009 Expert Panel, and many others:

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[2] Miller, B.G., Searl, A., Davis, J.M.G., Donaldson, K., Cullen, R.T., Bolton, R.E., Buchanan, D., and Soutar, C.A., "Influence of fiber length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity," *Ann Occup Hyg*, 1999a; 43(3): 155-66.

[3] Miller, B.G., Jones, A.D., Searl, A., Buchanan, D., Cullen, R.T., Soutar, C.A., Davis, J.M.G., and Donaldson, K., "Influence of characteristics of inhaled fibres on development of tumors in the rat lung," *Ann Occup Hyg*, 1999b; 43(3): 167-79.

> Studies that are considered most informative for assessment of carcinogenic potential of insulation glass wool and special purpose glass wool fibers are those conducted by the inhalation route of exposure and are listed below. Studies conducted by other routes for insulation glass wool and special purpose fibers are also listed but results of those studies are of limited usefulness for predicting human risk for inhalation of fibers.[4]

The companion Miller paper (Miller 1999b) states on page 177:

> Comparisons with results from intraperitoneal injection
>
> Our companion paper (Miller et al. 1999) describes the differences between these fibre types in their ability to induce mesothelioma production in the rat peritoneum, following injection of fixed numbers of fibers. Both that study and this have demonstrated relationships between fibre characteristics and cancer risks. For the intraperitoneal injection studies, numbers of long thin fibres and their biopersistence in the lung were the most important determinants. For the inhalation studies, the number of long thin fibres and the adjusted dissolution rate K_{dis} were the principal determining characteristics.

Notably, a discussion of the second Miller paper was not cited in the Draft Substance Profile but was specifically added to the Glass Wool Background Document by the Expert Panel Peer Review of that Draft document.[5]

The Expert Panel stated:

> Section 5.3.4 page 207 . . . The following discussion of Miller et al. 1999b and Eastes and Hadley 1996 should be added to this section;
>
> Miller et al. (1999a) examined the influence of fiber characteristic on tumor development in rat lungs for inhalation studies with the same set of 9 fiber types that they reported on for the intraperitoneal studies (Miller 1999a). The factors of fiber dimensions, persistence in the lung, dissolution *in vitro*, and cell toxicity *in vitro* were assessed. In the inhalation studies, the determining factors were the number of long, thin fibers (< 1 μm in diameter and > 20 μm long) and the dissolution rate adjusted for mass lost per unit initial mass. Short term cell toxicity tests *in vitro* were not significantly related to cancer risks in any model tested. The authors noted that the effect of dissolution rate rather than biopersistence in the lung was contrary to expectations, but they suggested that larger measurement error for *in vivo* biopersistence compared with *in vitro* dissolution might be responsible.

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[4] NTP, "Glass Wool Fibers Expert Panel Report, Part B – Recommendation for Listing Status for Glass Wool Fibers and Scientific Justification for the Recommendation," July 21, 2009, p. 8.
[5] NTP Glass Wool Fibers Expert Panel, Peer Review of Background Document, p. 25.

By failing to note the large dose differences in the intraperitoneal injection study in the first Miller 1999 study (Miller 1999a), and failing to even cite the inhalation-based study of the second Miller 1999 study (Miller 1999b), which supports the utility of K_{dis}, the Draft Substance Profile does not accurately or completely describe the important available scientific data.

An additional change to the Draft Substance Profile that would increase its usefulness is to add a brief sentence stating the dissolution rate is primarily a function of fiber composition. For example, Eastes, *et al.* (2000)[6] provided data on 62 glass compositions and presented a model for calculating K_{dis} from compositions (*see* Fig. 3). The adjusted value for R^2 is 0.955 for this sample and the 95 percent confidence interval includes unity.

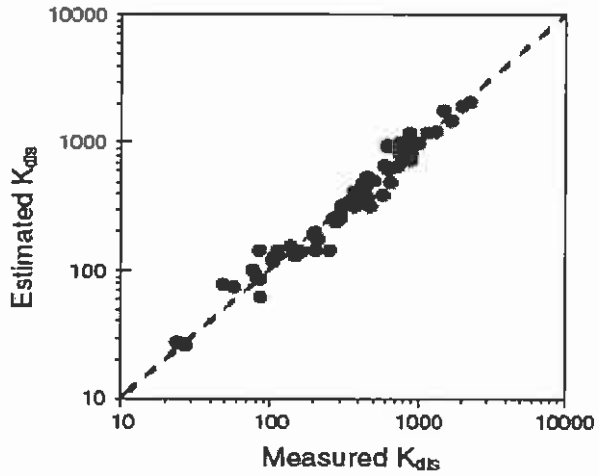

Fig. 3. Dissolution rate constant K_{dis}, calculated from fiber composition compared to measured value. The confidence interval on the least squares slope includes unity Eastes et al., 2000a.

Numerous papers are available on this topic. For a thorough review, see Maxim, *et al.* 2006.[7]

THE LIMITATIONS OF SHORT TERM IN VITRO BIOASSAY STUDIES OF FIBERS IS NOT MENTIONED

The Draft Substance Profile on page 5 states: "Glass wool fibers have the potential to cause genetic damage (Nguea *et al.* 2008)." It then discusses various studies illustrating such effects.

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[6] Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating In Vitro Glass Fiber Dissolution Rate from Composition," *Inhalation Toxicology* 12:269-280 (2000).

[7] Maxim, L.D., Hadley, J.G., et al., "The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology," *Regulatory Toxicology and Pharmacology*, 46(1): 42-62 (2006).

The Draft Substance Profile fails to note that none of these short term assays can account for the critical role of fiber biopersistence. Because the assays are conducted in just a few hours or, at most, days, they cannot distinguish between very soluble and very durable fibers. In effect, they assess only fiber size and number. The IARC 2002 Monograph stated: "Because biopersistence is believed to be an important factor in the toxicity of man-made vitreous fibers, there are limitations inherent in short-term *in vitro* assay of fiber toxicity."[8] Specifically regarding genetic effects, the Monograph states: "A major gap in the current database is the absence of any studies that correlate genotoxic end-points with the pathogenic effects of man-made vitreous fibres in the same experimental animal system."[9] The Expert Panel was reluctant to endorse short term *in vitro* bioassay studies and stated in its report that: "The data indicate that fibers have the potential to cause genetic damage *in vitro*. However, extrapolation from these data to carcinogenicity is problematic."[10]

Given the caveats noted by both IARC and the NTP Expert Panel on the utility of short term *in vitro* bioassays and their inability to account for fiber biopersistence, the Draft Substance Profile should at least acknowledge this issue by adopting these caveats in the Final Substance Profile.

UNSUPPORTED CONCERNS ABOUT BIOSOLUBLE FIBERS

To be complete and provide actionable information and data, the Final Substance Profile should address two issues that are sometimes raised regarding biosoluble fibers. The first is the allegation that inhaled biosoluble fibers have a potential for systemic toxicity. The second is the supposition that with daily exposure to fibers, even fibers that dissolve rapidly could be immediately replaced with newly arriving fibers resulting in fiber accumulation.

Both of these questions are addressed specifically in Maxim, *et al.* (2006),[11] so only a brief summary is provided here. Potential systemic toxicity should not be a concern as seen by simply considering the very small mass of an inhaled fiber. For example, at a concentration of 1 f/cc (a reasonable worst case at the higher end of occupational exposure)[12] with the fibers being 1 micron in diameter and 20 microns long, the mass of the 1 million fibers in a cubic meter of air would be only 40 micrograms. For the 10 cubic meters inhaled during a workday, the total inhaled mass would be only 400 micrograms. If one assumes 25 percent of the fibers were deposited in the lung, the total mass would be 100 micrograms per day. Contrast this to ACGIH TLV values for the common oxides in insulation glass wool fibers (ranging from 2-10 mg/c^3), and it can be determined that the inhaled fibers would contribute less than 1 percent of the daily amount inhaled at the TLV.

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[8] International Agency for Research on Cancer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Man-Made Vitreous Fibres*, Vol. 81 (Lyon, France: WHO/IARC, 2002), p. 336.
[9] *Ibid.* at p. 337.
[10] NTP Glass Wool Fibers Expert Panel Report, Part B, p. 12.
[11] Maxim at pp. 54-55.
[12] G.E. Marchant, et al., "A Synthetic Vitreous Fiber (SVF) Occupational Exposure Database: Implementing the SVF Health and Safety Partnership Program," *Applied Occupational and Environment Hygiene*, 17(4): 276-285, 2002.

The second question regarding the effect of the constant replacement of fibers with newly deposited fibers in the lungs also is not a realistic concern due to the anatomy of the human lung. Using the reasonable worst case scenario above, a worker would have 2.5 million fibers deposited in the lower lung in one work day. Since the human lung contains about 500 million alveoli, it would take over 6 months to achieve an average of 1 fiber per alveola. However, if one considers that it is the long (>20 microns) fibers that are of most concern, and if they represent 25 percent of the inhaled fibers, there would be about 625,000 fibers per work day spread among the 500 million alveoli. In this case, it would take over two years to achieve an average of 1 long fiber per alveola. Since insulation wool fibers dissolve or break transversely and are cleared in a matter of weeks or months, the concept of constant deposition and bioaccumulation of fibers in the alveoli is not correct.

In summary, the extensive database on the critical importance of the durability and biopersistence of insulation glass wool fibers is not presented in sufficient detail in the Draft Substance Profile. Given the importance of the topic, a more informative discussion is warranted in order for the Final Substance Profile to provide complete and actionable information and data.

Sincerely,

[Redacted]

John G. Hadley, Ph.D.

Enclosure: Appendix A

APPENDIX A
Comments of John G. Hadley, Ph.D., Owens Corning Corporation
Peer Reviewed Publications: Fiber Related

1. Maxim, L. D., Hadley, J. G., Potter, R. M., and Niebo, R., "The role of fiber durability/biopersistence of silica-based synthetic vitreous fibers and their influence on toxicology," *Regulatory Toxicology and Pharmacology,* 46(1): 42-62 (2006).

2. Bernstein, D.B., Castranova, V., Donaldson, K., Fubini, B., Hadley, J., Hesterberg, T.W., Kane, A., Lai, D., McConnell, E.E., Muhle, H., Oberdorster, G., Olin, S., and Warheit, D., "Testing of Fibrous Particles: Short-Term Assays and Strategies, Report of an ILSI Risk Science Institute Working Group," *Inhalation Toxicology*, 17:497-537 (2005).

3. Maxim, L.D., Eastes, W., Hadley J.G., Carter, C.M., Reynolds, J.W., Niebo, R., "Fiber glass and rock/slag wool exposure of professional and do-it-yourself installers," *Regulatory Toxicology and Pharmacology*, 37: 28-44 (2003).

4. Fayerweather, W.E., Eastes, W., Cereghini, F., Hadley, J.G., "Quantitative Risk Assessment of Durable Glass Fibers," *Inhalation Toxicology*, 14:553-568 (2002).

5. Eastes, W., and Hadley, J.G., "Comment on "Long Man-Made Fibers and Lung Cancer Risk," *Regulatory Toxicology and Pharmacology*, 33: 268 (2001).

6. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating Rock and Slag Wool Fiber Dissolution Rates from Composition," *Inhalation Toxicology*, 12:1127-1139 (2000).

7. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimation of Dissolution Rate from In Vivo studies of Synthetic Vitreous Fibers," *Inhalation Toxicology*, 12:1037-1054 (2000).

8. Eastes, W., Potter, R.M., and Hadley, J.G., "Estimating In Vitro Glass Fiber Dissolution Rate from Composition," *Inhalation Toxicology*, 12: 269-280 (2000).

9. Hesterberg, T.W, Chase, G., Axten, C., Miiller, W.C., Musselman, R.P., Kamstrup, O., Hadley, J. G., Morscheidt. C., Bernstein, D.M. and Thevenaz, P., "Biopersistence of Synthetic Vitreous Fibers and Amosite Asbestos in the Rat Lung following Inhalation," *Toxicology and Applied Pharmacology*, 151, 262-275 (1998).

10. Fayerweather, W., E., Bender, J.R., Hadley, J.G., Eastes, W., "Quantitative Risk Assessment for a Glass Fiber Insulation Product," *Regulatory Toxicology and Pharmacology*, 25: 103-120 (1997).

11. Eastes, W., Hadley, J.G. and Bender, J., "Assessing the Biological Activity of Fibers: Insights into the Role of Fiber Durability," *Australian/NZ Journal of Occupational Health and Safety*, 12(3): 381-385 (1996).

12. McConnell, E.E., Hesterberg, T, Chevalier, J., Thevenaz, P., Kotin, P., Mast, R., Musselman, R., Kamstrup, O., Hadley, J., "Results Of Life-Time Inhalation Studies of Glass, Mineral and Slag Wools and Refractory Ceramic Fibers in Rodents," *Australian/NZ Journal of Occupational Health and Safety*, 12(3): 327-332 (1996).

13. Eastes, W., Hadley. J.G, "A Mathematical Model of Fiber Carcinogenicity and Fibrosis in Inhalation and Intraperitoneal Experiments in Rats," *Inhalation Toxicology*, 8:323-343 (1996).

14. Eastes, W., Hadley, J.G., "Dissolution of Fibers Inhaled by Rats," *Inhalation Toxicology*, 7:179-196 (1995).

15. Eastes, W., Morris, K.J., Morgan, A., Launder, K.A., Collier, C.G., Davis, J.A., Mattson, S.M., Hadley, J.G., "Dissolution of Glass Fibers in the Rat Lung Following Intratracheal Instillation," *Inhalation Toxicology*, 7:197-213 (1995).

16. Eastes, W., Hadley, J.G., "Role of Fiber Dissolution in Biological Activity in Rats," *Regulatory Toxicology and Pharmacology*, 20: S104-S112 (1994).

17. Bender, J.R., Hadley, J.G., "Glass fiber Manufacturing and Fiber Safety: The Producers Perspective," *Environmental Health Perspectives*, 102: Supplement 5, 37-40 (1994).

18. Bernstein, D.B., Mast, R., Anderson, R., Hesterberg, T.W., Musselman, R., Kampstrup, O., Hadley, J.G., "An Experimental Approach to the Evaluation of the Biopersistence Of Respirable Synthetic Fibers and Minerals," *Environmental Health Perspectives*, 102 Supplement 5, 15-18 (1994).

19. Musselman, R.,P., Miiller, W. C., Eastes, W., Hadley, J.G., Kamstrup, O., Thevanez, P., and Hesterberg, T.W., "Biopersistence of Man-Made Vitreous Fibers and Crocidolite Fibers in Rat Lungs Following Short Term Exposure," *Environmental Health Perspectives*, 102 Supplement 5, 139-144 (1994).

20. Hesterberg, T.W., Miiller, W.C., McConnell, E.E., Chevalier, J.G. Hadley, J.G., Bernstein, D.M., Thevanez, P., and Anderson, R,, "Chronic Inhalation Toxicity of Size Separated Glass Fibers in Fischer 344 Rats," *Fundamental and Applied Toxicology*, 20:464-476 (1993).

21. Jacob, T.R., Hadley, J.G., Bender, J.R., Eastes, W., "Airborne Glass Fiber Concentrations during Manufacturing Operations Involving Glass Wool Insulation," *American Industrial Hygiene Association Journal*, 54: 320-326 (1993).

22. Jacob, T.R., Hadley, J.G., Bender, J.R., Eastes, W., "Airborne Glass Fiber Concentrations during Installation of Residential Insulation," *American Industrial Hygiene Association Journal*, 53:519-523 (1992).